Firenze, 16th September 2016

Novita da EHA 2016 – Copenhagen

Linfomi
THREE QUESTIONS TO ADDRESS:

1. Is ASCT still the golden standard for MCL? And how to challenge it in the future?

2. What is new in relapsed follicular lymphoma? Is benda-obinotuzumab a major step forward? Which are the alternatives?

3. Ultra high-risk lymphoma patients: Can we identify them? And where shall we go for treatment?
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### Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up


<table>
<thead>
<tr>
<th>Young patient (≤65)</th>
<th>Elderly patient (&gt;65)</th>
<th>Compromised patient</th>
</tr>
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<tbody>
<tr>
<td>First line treatment</td>
<td>Conventional immuno-chemotherapy (e.g. R-CHOP, BR)</td>
<td>Watch and wait? R-Chlorambucil BR</td>
</tr>
<tr>
<td>Dose-intensified Immuno-chemotherapy (R-CHOP + R-high dose Ara-C) (alternating or sequential) =&gt; ASCT</td>
<td>Rituximab maintenance radioimmunotherapy</td>
<td></td>
</tr>
</tbody>
</table>

### 1. Relapse

<table>
<thead>
<tr>
<th>High tumour load: Immuno-chemotherapy (e.g. BR, R-DHAP)</th>
<th>Immuno-chemotherapy (e.g. BR, R-FC) Targeted approaches</th>
<th>Immuno-chemotherapy (e.g. BR) Targeted approaches</th>
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</thead>
<tbody>
<tr>
<td>Allo-transplant Radioimmunotherapy Rituximab maintenance</td>
<td>ASCT Radioimmunotherapy Rituximab maintenance</td>
<td></td>
</tr>
</tbody>
</table>

### Higher relapse

- Targeted approaches: Temsirolimus, Bortezomib*, Ibrutinib, Lenalidomide* (preferable in combination)
- Repeat previous therapy (long remissions)

R, rituximab; CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; B, bendamustine; FC, fludarabine/cyclophosphamide; ASCT, autologous stem-cell transplantation; *currently not registered in this indication in the European Union (EU).
Points raised by prof E Zucca in the educational session EHA2016

Copenhagen

1. Watch and wait?

2. Prognosticators and prognostic models

3. Role of MRD

4. Role of PET
Conclusions from prof T. Robak in the educational session EHA2016

Copenhagen

1. Heterogeneity and personalization

2. OS is improving

3. Target drugs are effective in the R/R setting

4. Auto ASCT and allo-SCT should be considered also at relapse
The role of targeted treatment in mantle cell lymphoma: is transplant dead or alive?

Martin Dreyling\textsuperscript{1} and Simone Ferrero,\textsuperscript{2} on behalf of European Mantle Cell Lymphoma Network

\textsuperscript{1}Department of Medicine III, Hospital of the University LMU München, Germany; and \textsuperscript{2}Division of Hematology, Department of Molecular Biotechnologies and Health Sciences, University of Torino, Italy

Haematologica, 2016
YOUNG PATIENTS PROBABLY NOT DESERVING ASCT

✓ Patients with major comorbidities
✓ Patients with limited stage MCL
✓ Indolent MCL
✓ Primary refractory patients

For specific prognostic subgroups…. NOT YET
Table 1. Published clinical studies investigating first-line dose-intensified therapy in MCL.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Features</th>
<th>Evaluable patients</th>
<th>Therapeutic regimen</th>
<th>ORR% (CR%)</th>
<th>Median PFS (years)</th>
<th>Median OS (years)</th>
<th>Dropout rate</th>
<th>TRM</th>
<th>Secondary tumors rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dreyling et al., 2005</td>
<td>Phase III, randomized</td>
<td>122</td>
<td>R-CHOP + TBI + ASCT vs. R-CHOP + TBI + interferon-α</td>
<td>98 (81) vs. 99 (37)</td>
<td>3,3 vs. 1,4</td>
<td>NR (83% 3-y OS) vs. NR (77% 3-y OS)</td>
<td>13% vs. 5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Hermine et al., 2012</td>
<td>Phase III, randomized</td>
<td>455</td>
<td>R-CHOP + TBI + ASCT vs. R-CHOP/R-DHAP + HD-araC + ASCT</td>
<td>98 (63) vs. 99 (61)</td>
<td>3,8 vs. 7,3</td>
<td>NR</td>
<td>na</td>
<td>4%</td>
<td>na</td>
</tr>
<tr>
<td>Damon et al., 2009</td>
<td>Phase II</td>
<td>77</td>
<td>R-CHOP + methotrexate + HD-araCetoposide + ASCT</td>
<td>88 (69)</td>
<td>NR (56% 5-y PFS)</td>
<td>NR</td>
<td>13%</td>
<td>3%</td>
<td>na</td>
</tr>
<tr>
<td>Van't Veer et al., 2009</td>
<td>Phase II</td>
<td>87</td>
<td>R-CHOP + HD-araC + ASCT</td>
<td>70 (64)</td>
<td>NR (36% 4-y OS)</td>
<td>NR</td>
<td>30%</td>
<td>5%</td>
<td>na</td>
</tr>
<tr>
<td>Geisler et al., 2012</td>
<td>Phase II</td>
<td>160</td>
<td>R-Maxi-CHOP + HD-araC + ASCT</td>
<td>96 (54)</td>
<td>7,4</td>
<td>NR</td>
<td>9%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Delarue et al., 2013</td>
<td>Phase II</td>
<td>60</td>
<td>R-CHOP/R-DHAP + HD-araC + ASCT</td>
<td>100 (96)</td>
<td>6,9</td>
<td>NR</td>
<td>18%</td>
<td>1,5%</td>
<td>18%</td>
</tr>
<tr>
<td>Touzeau et al., 2013</td>
<td>Retrospective</td>
<td>396</td>
<td>Different ASCT-based schedules</td>
<td>83 (77)</td>
<td>NR (67% 3-y PFS)</td>
<td>NR</td>
<td>na</td>
<td>2,5%</td>
<td>6%</td>
</tr>
<tr>
<td>Kolstad et al., 2014</td>
<td>Phase II</td>
<td>160</td>
<td>R-Maxi-CHOP + HD-araC + Zevalin + ASCT</td>
<td>94 (82)</td>
<td>CR (71% 4-y PFS)</td>
<td>NR (78% 4-y OS)</td>
<td>9%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Le Gouill et al., 2014</td>
<td>Phase III, randomized</td>
<td>299</td>
<td>R-DHAP + ASCT +/- rituximab maintenance</td>
<td>na (92)</td>
<td>CR (74% 3-y PFS)</td>
<td>NR (83% 3-y OS)</td>
<td>14%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Cortelazzo et al., 2015*</td>
<td>Phase III, randomized</td>
<td>260*</td>
<td>R-CHOP+R-CTX+HD-araC+ASCT +/- lenalidomide maintenance</td>
<td>86 (78)</td>
<td>CR (78% 2-y OS)</td>
<td>NR (89% 2-y OS)</td>
<td>22%*</td>
<td>2%</td>
<td>na</td>
</tr>
<tr>
<td>Romaguera et al., 2010</td>
<td>Phase II, monocentric</td>
<td>97</td>
<td>R-Hyper-CVAD</td>
<td>97 (87)</td>
<td>4,5</td>
<td>NR</td>
<td>29%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Merli et al., 2012</td>
<td>Phase II, multicentric</td>
<td>60</td>
<td>R-Hyper-CVAD</td>
<td>83 (72)</td>
<td>CR (73% 5-y PFS)</td>
<td>NR</td>
<td>63%</td>
<td>6,5%</td>
<td>1,5%</td>
</tr>
<tr>
<td>Bernstein et al., 2013</td>
<td>Phase II, multicentric</td>
<td>49</td>
<td>R-Hyper-CVAD</td>
<td>86 (55)</td>
<td>4,8</td>
<td>6,8</td>
<td>39%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Adapted from Dreyling M and Ferrero S, 2016
MRD response after induction

Elderly
- RR: 86%
- CR: 34%
- MRD: 78%
- MRD+: 40%

Younger
- RR: 90%
- CR: 25%
- MRD: 94%
- MRD+: 38%

RR: 86%
CR: 34%
MRD: 78%
MRD+: 40%

RR: 90%
CR: 25%
MRD: 94%
MRD+: 38%

Courtesy of Christiane Pott
15-YEAR FOLLOW-UP OF THE NORDIC MCL2-TRIAL: DESPITE LONG-TERM RESPONSES LATE RELAPSES STILL OCCUR

BACKGROUND

• Outcome of MCL has improved thanks to Ara-C and R
• the Nordic trial showed a projected 10-year OS and PFS of 58% and 43%
• Updated results at a median follow-up of 11.4 years

METHODS

• 160 untreated stage II-IV MCL pts.
• maxi-CHOP alternated to high-dose Ara-C, BEAM/BEAC and ASCT in responders (n=145).
• Use of pre-emptive rituximab (Andersen, JCO, 2009)

RESULTS

▪ the median OS and PFS were 12.7 and 8.5 years.
▪ RD of the 145 patients who underwent ASCT was 12.4 years
▪ micro-RNA-18b (MIPI-B-miR) remains highly significant and identifies a high-risk group of an exceedingly poor prognosis with OS and PFS of only 1.6 and 1.0 years
CONCLUSIONS

- A pattern of continuing relapse is observed, seemingly precluding cure.

- MIPI, MIPI-B and, in particular, MIPI-B-miR remain valid prognosticators that clearly separate patients into risk groups with different outcomes.

- All risk groups might benefit from addition of novel agents.
Rule S et al S438
OS OUTCOMES IN PTS WITH MCL TREATED WITH IBRUTINIB IN A POOLED ANALYSIS OF 370 PATIENTS FROM 3 INTERNATIONAL OPEN-LABEL STUDIES

BACKGROUND
• Pooled analysis from 3 ibrutinib studies (PCYC-1104, MCL2001 [SPARK] and MCL3001 [RAY])

METHODS
• Ibrutinib 560 mg orally
• Inclusion and exclusion criteria were similar
• Simple descriptive statistics and exploratory analyses were done for PFS and OS with univariate and multivariate analyses

RESULTS
• 370 patients were included in this analysis; median age was 67.5 years, 94%.
• 27%, 29%, 22% had 1, 2, 3 prior lines of therapy.
• Overall response rate (ORR) was 66% (20% CR; 46% PR),
• ORR for patients with 1, 2 and ≥3 prior lines of therapy was 77%, 71% and 64%
• DOR, PFS and OS of 18.6, 12.8 and 25.0 months,
• CR pts, had a PFS of 70% and OS of 90% at 2 years.
• ECOG, sMIPI, bulky disease and blastoid histology impacts OS
CONCLUSIONS

OS is better patients who are younger and who have fewer prior lines of therapy

Ibrutinib is an effective agent in blastoid MCL to achieve a response and potentially provide a bridge transplant.

Data support the preferential use of ibrutinib after initial vs later relapse
NPP program to allow access to ibrutinib for eligible patients R/E MCL. This program provides real-world data on estimated outcomes with ibrutinib across a large, global MCL population.
BACKGROUND

• To identify specific mechanisms of ibrutinib resistance in MCL, and to correlate genetic signatures with patient response.

METHODS

• Primary resistance analysis,
• Acquired resistance analysis.

RESULTS

Mutations associated with primary resistance to ibrutinib were identified in NF-κB signaling pathways, both canonical (e.g., A20) and non-canonical (e.g., BIRC2). Other mutations were found in epigenetic modifiers and in the EGFR family.

Acquired resistance: Mutations in epigenetic modifiers and alternate NF-κB or PI3K/mTOR pathways were found after a short treatment duration (<4 months).

No primary or secondary BTK C481S mutations

CONCLUSIONS

Understanding both primary and acquired resistance patterns is key in order to improve outcomes and define the populations that benefit from ibrutinib treatment.
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BACKGROUND
FL subset analysis of GADOLIN pts. 321 (81%) of 396 iNHL pts enrolled had FL.

METHODS
Pts received either G + B90 or B120

RESULTS
Median number of prior therapies was 2. 94% pts were refractory to their last prior rituximab (R)-containing regimen and 88% double-refractory to R and an alkylating agent.

According to IRC PFS is not reached in the G-B arm and 13.8 mo in the B arm (Figure 1),

Survival data were immature at the time of analysis. Safety profiles were comparable.
Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FL subpopulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G-B (n=155)</td>
</tr>
<tr>
<td>Median observation time (range), mo</td>
<td>22.08 (0.4-48.5)</td>
</tr>
<tr>
<td><strong>PFS (IRC)</strong></td>
<td></td>
</tr>
<tr>
<td>Pts with event, n (%)</td>
<td>54 (34.8)</td>
</tr>
<tr>
<td>Median (mo)</td>
<td>Not reached</td>
</tr>
<tr>
<td>HR [95% CI]; stratified*</td>
<td>0.48 [0.34-0.68]</td>
</tr>
<tr>
<td><strong>PFS (INV)</strong></td>
<td></td>
</tr>
<tr>
<td>Pts with event, n (%)</td>
<td>62 (40.0)</td>
</tr>
<tr>
<td>Median (mo)</td>
<td>29.2</td>
</tr>
<tr>
<td>HR [95% CI]; stratified*</td>
<td>0.48 [0.35-0.67]</td>
</tr>
<tr>
<td><strong>Response† (IRC)</strong></td>
<td></td>
</tr>
<tr>
<td>EOL response (%); overall†/CR</td>
<td>70.5/9.4</td>
</tr>
<tr>
<td>Best response (%); overall†/CR</td>
<td>79.7/15.7</td>
</tr>
</tbody>
</table>

*Stratification factors for FL population were refractory type (R vs R-chemo) and prior therapies (≤2 vs >2); † During treatment and within 12 mo after start of treatment; ‡ Complete response (CR) or partial response.
ANALYSIS OF SECONDARY NEOPLASIAS AFTER HIGH DOSE THERAPY SUPPORTED BY AUTOLOGOUS STEM CELL TRANSPLANTATION IN FOLICULAR LYMPHOMA PATIENTS. A LONG TERM FOLLOW-UP ANALYSIS FROM THE GELTAMO REGISTRY.

BACKGROUND

• HDT/ASCT is effective in FL
• Secondary neoplasia is one of the major concerns

To evaluate the cumulative incidence and characteristics of sMDS/sAML and solid tumors after HDT/ASCT in a very long-term follow-up analysis of FL patients.

METHODS

A total of 655 FL patients (GELTAMO registry)

RESULTS

Median follow-up 12 years. The median OS were 21.3 years from HDT/ASCT and 22.6 years from the time of FL diagnosis. 12.5% developed a second malignancy: solid tumors (47.5%), sMDS/sAML (42.5%). The accumulated incidence at 5, 10 and 15 years was 1.8%, 3.5% and 4.9% for solid tumors and 2.6%, 4.3% and 5% for sMDS/sAML. Male sex and BM as stem cell source were associated to an increased risk.
CONCLUSIONS
FL pts are at an increased risk of second malignancy but not as high as reported.

Low percentage of TBI and early transplant could explain these good results.

Once a secondary neoplasia is diagnosed prognosis is dismal.

the incidence of secondary neoplasia will probably not diminish the benefit of HDT/ASCT in relapsed FL.
RESULTS
413 pts enrolled. Good safety confirmed.
**ORR in 354 evaluable pts was 76.8%, CR rate 47.7%.**
ORR and CR for those receiving 2 or less prior regimens were 86.0% and 56.1% respectively, while
ORR and CR for those receiving more than 2 prior regimens were 69.3% and 40.7%

CONCLUSIONS
90YITis a tolerable and efficacious treatment option for pts with R/R B-cell NHL or MCL in Japan,
It demonstrates good benefit-risk balance
RESULTS  Results: 66 pts with refractory FL who had documented prior treatment regimens. A total of 12 pts (20%) ASCT.

With a median follow up of 109 days IDELA monotherapy was well-tolerated with 6/66 pts (9.1%) reporting an SAE.

(Febrile neutropenia, neutropenia, diarrhea, gastrointestinal inflammatory disorder, pancytopenia, progressive disease, liver enzyme elevation, hypotension and colon cancer).

CONCLUSIONS: The results confirm the acceptable tolerability profile of IDELA.
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BACKGROUND

The TMTV assessed on the baseline FDG-PET assessed prospectively in pts enrolled in a phase III randomized trial (PET-driven)

RESULTS

• follow-up of 16 months, 2y-PFS was 81% vs 93% in pts with high and low TMTV

• Using also PET-2 3 groups could be identified having a 61%, 88%, 94% 2y-PFS respectively (p<0.0001).

CONCLUSIONS

The TMTV predicts the outcome of young advanced HL pts. The combination of TMTV and PET2 allows identifying 3 subsets of HL pts
BACKGROUND
To determine clinical and molecular predictors of EFS and OS for rrDLBCL pts treated with R-GDP or R-DHAP followed by ASCT (Canadian Ly12 study)

METHODS
91 pts had DLBCL immunohistochemical (IHC) testing for CD10, BCL6, MUM1, FOXP1, LMO2, BCL2, CMYC, P53, pySTAT3 expression.

In addition, 97 formalin-fixed, had GEP with NanoString to evaluate Cell of Origin (COO) by the Lymph2Cx assay, as well as BCL2, MYC, P53, STAT3, PDL1 and PD1 expression.

RESULTS
• Expression of both MYC and BCL2 was associated to poor outcome. Dual expressing (DE) lymphomas (MYC+/BCL+) had significantly worse 3y EFS (0% vs 40%, p=0.0009) and OS rates (20% vs 54%, p=0.0004)
MYC and BCL2 expression using NanoString GEP (>1.5xmean) were significantly associated with inferior OS and EFS, and no patient who expressed both markers achieved 2y EFS or OS.

Concordance rate of 79% was seen for MYC and 57% for BCL2. In multivariate analyses, primary refractory DLBCL, LDH at relapse, MYC expression and BCL2 expression (assessed by either IHC or GEP).

**CONCLUSIONS**

MYC and BCL2 expression, determined by IHC or Nanostring GEP, are independent poor prognostic factors for rrDLBCL, and dual expression predicts dismal prognosis.
BACKGROUND
PBL remains a diagnostic and therapeutic challenge with an aggressive clinical course. Aim of this study was to specify the clinical, biological, pathological features and outcome of patients with PBL.

METHODS AND RESULTS

135 patients with PBL diagnosed after 2000 within LYSA. The median age was 58, male predominance. 56 HIV-positive patients, 17 post-transplant patients, and 62 “immunocompetent”.

However also this subtype of patients may present some degree of immunodepression.

Immunophenotype showed CD138 positivity in 88% of cases and CD20 negativity in 90% of cases. EBER expression was observed in 62% of cases. Chemotherapy was administered to 108 of 135 patients, with a complete response rate of 55%. Rituximab, had a trend towards improved CR rate. The median overall survival was 32 mos. HIV positive status showed better overall survival.

DISCUSSION
Specific guidelines to clarify all the treatment options are lacking
BACKGROUND

allo-HCT has been used in RR HL with controversial results. Aim of our study is to investigate the role of allo-HCT in RR HL

METHODS

69 patients with RR HL, median age 34 (range, 18 - 64), 52 patients (75%) were at least in PR. The remaining 16 patients (23%) had progressive disease (non-responsive).

Brentuximab Vedotin (BV) was given as bridge to transplant in 11 patients. Moreover, 7 patients received BV after allo-HCT.

The majority of patients underwent reduced intensity allo-HCT, 64 patients (93%). MUD in 57%. The stem cells source was PB in 61 patients (88%).
RESULTS

Median OS of 5.1 years (range, 0 - 13.8) and RFS of 1.3 years.

The 5-year cumulative incidence of treatment related mortality (TRM) and relapse were 17.7% and 43.4%, respectively.

The 5-year estimated of RFS was significantly higher in responsive compared to non-responsive patients, 46.9% versus 12.5%, respectively, p= 0.009.

Eleven patients received BV as bridge to allo-HCT for a median of 6 cycles. All patients achieved at least PR. None of patients treated with BV had unexpected toxicity or GVHD worsening.

DISCUSSION

Allo-HCT is a feasible and effective option for RR HL.

BV showed efficacy as a bridge to allo- HCT as well as post allo-HCT rescue.
CHALLENGING HIGH-RISK PATIENTS

TRADITIONAL BACKBONE TREATMENT

- Poor diagnostic profile
- Failure to achieve MRD/PET negativity or MRD loss

Innovative or potentiated treatment
THANK YOU FOR YOUR ATTENTION!!!

HAVE AN EXCITING AND FRUITFUL DISCUSSION !!!!
**TRIANGLE study**

**Flow chart**

**Figure 2: Study flow chart**

**Induction**

- Standard Arm A: R-CHOP/R-DHAP followed by ASCT
- Experimental Arm A+: R-CHOP/R-DHAP + I followed by ASCT and I-maintenance
- Experimental Arm I: R-CHOP/R-DHAP + I followed by I-maintenance

**ASCT / Maintenance / Observation**

- Observation until end of the study.
- Observation up to 7.5 years.
- Observation up to 7.6 years.

**Initial Staging, Randomization**

- Rituximab
- CHOP
- DHAP
- Ibrutinib

**ASCT:** THAM or BEAM

**Staging timepoints:** CT - mandatory, MRD and optional PET
- Initial: Before randomization
- Midterm: after 4 cycles
- End of induction: after 6 cycles
- ASCT: 4-6 weeks after ASCT

**SD, PD:** no study specific treatment follow-up for survival
Any salvage treatment

Arm A: consolidation with RIT
- Rituximab maintenance every three months for 8 courses (starting three months after consolidation)
- At relapse
  - ASCT With Previously collected PBSC

Arm B: consolidation with ASCT
- Rituximab maintenance every three months for 8 courses (starting three months after consolidation)
- At relapse

BLIND RANDOMIZATION
Pts stratified based on Center characteristics and response

ARA-C 2g/sqm b.i.d. 2 days with Rituximab in vivo purging

Randomization unblinding

MRD

3 R-CHEMO REGIMENS
(R-CHOP, R-DHAP, R-FM, R-ICE, R-IEV, R-B)

MRD

CR-PR

SD-PD

MRD

MRD

MRD
 protocols in relapsed FL: Renoir

A randomized phase III multicenter trial assessing efficacy and toxicity of a combination of Rituximab and Lenalidomide (R2) vs Rituximab alone as maintenance after chemoimmunotherapy with Rituximab-Bendamustine for relapsed/refractory FL patients not eligible for autologous transplantation (ASCT).

RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA NEED TO THERAPY

R-Bendamustine x 4 once a month
Rituximab 375 mg/m² day 0 or 1 (day 8 on cycle 1)
Bendamustine 90 mg/m² iv days 1-2

CR/PR  →  NR  →  OFF

Random

R2
Rituximab 375 mg/m² day 1 q 90 days (8 cycles)
Lenalidomide (10 mg dd 1-21 q 28) (24 cycles)

R alone
Rituximab 375 mg/m² day 1 q 90 days (8 cycles)